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(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SCOTT, Robert, Andrew, Donald [ZA/US]; 302 Riverside Avenue, Riverside, CT 06878 (US).

(74) Agents: SPIEGEL, Allen, J.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.

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(54) Title: COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT

(57) Abstract

This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby those synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.

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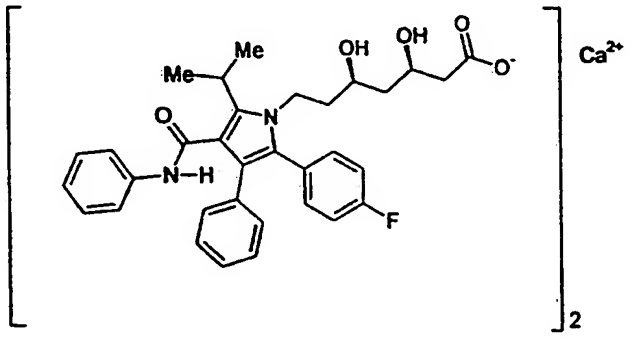
COMBINATION THERAPY COMPRISING ATORVASTATIN AND AN ANTIHYPERTENSIVE AGENT

This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby those additive and synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms or signs of cardiac risk, including humans.

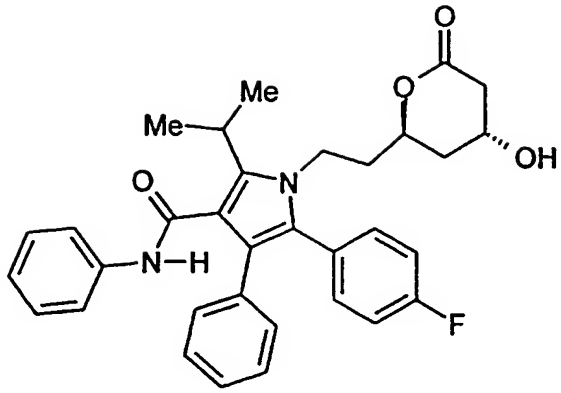
BACKGROUND OF THE INVENTION

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reducatase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents.

Atorvastatin calcium, disclosed in U.S. Patent No. 5,273,995, which is incorporated herein by reference, is currently sold as Lipitor® and has the formula



Atorvastatin calcium is a selective, competive inhibitor of MG-CoA. As such, atorvastatin calcium is a potent lipid lowering compound. The free carboxylic acid form of atorvastatin exists predominantly as the lactone of the formula:



and is disclosed in U.S. Patent No. 4,681,893, which is incorporated herein by reference.

Several classes of compounds are known to have activity as antihypertensive agents. These include calcium channel blockers, ACE inhibitors, A-II antagonists, diuretics, beta-adrenergic receptor blockers, vasodilators and alpha-adrenergic receptor blockers.

Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries. Atherosclerotic coronary heart disease (hereinafter termed "CHD") accounts for 53% of all deaths attributable to a cardiovascular event. CHD accounts for nearly one-half (about $50-60 billion) of the total U.S. cardiovascular healthcare expenditures and about 6% of the overall national medical bill each year. Despite attempts to modify secondary risk factors such as, *inter alia*, smoking, obesity and lack of exercise, and treatment of dyslipidemia with dietary modification and drug therapy, CHD remains the most common cause of death in the United States.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. It is well known that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (Brown and Goldstein, New England Journal of Medicine, 1981, 305, No. 9, 515-517). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (see, e.g., The Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 1994, 344, 1383-

89; and Shepherd, J. et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, New England Journal of Medicine, 1995, 333, 1301-07).

Angina pectoris is a severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. Often angina pectoris is due to ischemia of the heart and is usually caused by coronary disease.

Currently the treatment of symptomatic angina pectoris varies significantly from country to country. In the U.S., patients who present with symptomatic, stable angina pectoris are frequently treated with surgical procedures or PTCA. Patients who undergo PTCA or other surgical procedures designed to treat angina pectoris frequently experience complications such as restenosis. This restenosis may be manifested either as a short term proliferative response to angioplasty-induced trauma or as long term progression of the atherosclerotic process in both graft vessels and angioplastied segments.

The symptomatic management of angina pectoris involves the use of a number of drugs, frequently as a combination of two or more of the following classes: beta blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid lowering agent as well. The National Cholesterol Education Program (NCEP) recognizes patients with existing coronary artery disease as a special class requiring aggressive management of raised LDL-C.

Amlodipine helps to prevent myocardial ischemia in patients with exertional angina pectoris by reducing Total Peripheral Resistance, or afterload, which reduces the rate pressure product and thus myocardial oxygen demand at any particular level of exercise. In patients with vasospastic angina pectoris, amlodipine has been demonstrated to block constriction and thus restore myocardial oxygen supply. Further, amlodipine has been shown to increase myocardial oxygen supply by dilating the coronary arteries.

Hypertension frequently coexists with hyperlipidemia and both are considered to be major risk factors for developing cardiac disease ultimately resulting in adverse cardiac events. This clustering of risk factors is potentially due to a common mechanism. Further, patient compliance with the management of hypertension is generally better than patient compliance with hyperlipidemia. It would therefore be

advantageous for patients to have a single therapy which treats both of these conditions.

Coronary heart disease is a multifactorial disease in which the incidence and severity are affected by the lipid profile, the presence of diabetes and the sex of the subject. Incidence is also affected by smoking and left ventricular hypertrophy which is secondary to hypertension. To meaningfully reduce the risk of coronary heart disease, it is important to manage the entire risk spectrum. For example, hypertension intervention trials have failed to demonstrate full normalization in cardiovascular mortality due to coronary heart disease. Treatment with cholesterol synthesis inhibitors in patients with and without coronary artery disease reduces the risk of cardiovascular morbidity and mortality.

The Framingham Heart Study, an ongoing prospective study of adult men and women, has shown that certain risk factors can be used to predict the development of coronary heart disease. (see Wilson et al., Am. J. Cardiol. **1987, 59(14)**:91G-94G). These factors include age, gender, total cholesterol level, high density lipoprotein (HDL) level, systolic blood pressure, cigarette smoking, glucose intolerance and cardiac enlargement (left ventricular hypertrophy on electrocardiogram, echocardiogram or enlarged heart on chest X-ray). Calculators and computers can easily be programmed using a multivariate logistic function that allows calculation of the conditional probability of cardiovascular events. These determinations, based on experience with 5,209 men and women participating in the Framingham study, estimate coronary artery disease risk over variable periods of follow-up. Modeled incidence rates range from less than 1% to greater than 80% over an arbitrarily selected six year interval. However, these rates are typically less than 10% and rarely exceed 45% in men and 25% in women.

Kramsch et al., Journal of Human Hypertension (1995) (Suppl. 1), 53-59 discloses the use of calcium channel blockers, including amlodipine, to treat atherosclerosis. That reference further suggests that atherosclerosis can be treated with a combination of amlodipine and a lipid lowering agent. Human trials have shown that calcium channel blockers have beneficial effects in the treatment of early atherosclerotic lesions. (see, e.g., Lichtlen, P.R. et al., Retardation of angiographic progression coronary artery disease by nifedipine, Lancet, 1990, 335, 1109-13; and Waters, D. t al., A controlled clinical trial to assess the effect of a calcium channel

blocker on the progression of coronary atherosclerosis, Circulation, 1990, 82, 1940-53.) U.S. 4,681,893 discloses that certain statins, including atorvastatin, are hypolipidemic agents and as such are useful in treating atherosclerosis. Jukema et al., Circulation, 1995 (Suppl. 1), 1-197disclose that there is evidence that calcium channel blockers act synergistically in combination with lipid lowering agents (e.g., HMG-CoA reductase inhibitors), specifically pravastatin. Orekhov et al., Cardiovascular Drugs and Therapy, **1997, 11**, 350 disclose the use of amlodipine in combination with lovastatin for the treatment of atherosclerosis.

SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition, hereinafter termed "Composition A", comprising:

a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof;

b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof; and

c. a pharmaceutically acceptable carrier or diluent;

provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition AA" of Composition A wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker, a vasodilator or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition AB", of Composition AA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a pharmaceutical composition, hereinafter termed "Composition AC", of Composition AB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

This invention is still more particularly directed to a pharmaceutical composition of composition AC wherein said calcium channel blocker is felodipine or nifedipine.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or trandolapril.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is also more particularly directed to a pharmaceutical composition of Composition AB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin or trimazosin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition B", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antiphypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition BA", of Composition B wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition BB", of Composition BA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a pharmaceutical composition, hereinafter termed "Composition BC", of Composition BB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker

being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

This invention is still more particulary directed to a pharmaceutical composition of Composition BC wherein said calcium channel blocker is felodipine or nifedipine.

This invention is still more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or trandolapril.

This invention is still more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is also more particularly directed to a pharmaceutical composition of Composition BB wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin or trimazosin.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition C", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition CA", of Composition C wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition CB", of Composition CA comprising the hemicalcium salt of atorvastatin.

This invention is still more particularly directed to a pharmaceutical composition hereinafter termed "Composition CC", of Composition CB wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

This invention is still more particularly directed to a pharmaceutical composition of Composition CC wherein said calcium channel blocker is felodipine or nifedipine.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or trandolapril.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

This invention is also more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

This invention is still more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

This invention is still more particularly directed to a pharmaceutical composition of Composition CB wherein said antihypertensive agent is an alpha-adren rgic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin or trimazosin.

This invention is also particularly directed to a pharmaceutical composition of Composition B wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is particularly directed to a pharmaceutical composition of Composition BB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also particularly directed to a pharmaceutical composition of Composition C wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also particularly directed to a pharmaceutical composition of Composition CB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition D", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition DA", of Composition D wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition DB", of Composition DA wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

This invention is also particularly directed to a pharmaceutical composition of Composition D wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a pharmaceutical composition of Composition DB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition E", for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a pharmaceutical composition, hereinafter termed "Composition EA", of Composition E wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is more particularly directed to a pharmaceutical composition, hereinafter termed "Composition EB", of Composition EA comprising the hemicalcium salt of atorvastatin.

This invention is also particularly directed to a pharmaceutical composition of Composition E wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also particularly directed to a pharmaceutical composition of Composition EB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipid mic; or is ffective for cardiac risk management.

This invention is also directed to a kit, hereinafter termed "Kit A", for achieving a therapeutic effect in a mammal comprising:

a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. container means for containing said first and second dosage forms, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a kit, hereinafter termed "Kit AA", of Kit A comprising the hemicalcium salt of atorvastatin.

This invention is more particularly directed to a kit, hereinafter termed "Kit AB", of Kit AA wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

This invention is still more particularly directed to a kit of Kit AB wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

This invention is also directed to a method, hereinafter termed "Method A", for treating a mammal in need of therapeutic treatment comprising administering to said mammal

(a) an amount of a first compound, said first compound being atorvastatin or a pharmaceutically acceptable salt thereof; and

(b) an amount of a second compound, said second compound being an antihypertensive agent or a pharmaceutically acceptable salt thereof;

wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

This invention is particularly directed to a method, hereinafter termed "Method AA", of Method A comprising the hemicalcium salt of atorvastatin.

This invention is more particularly directed to a method, hereinafter termed "Method AB", of Method AA wherein said antihypertensive agent is a calcium chann l

blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker, or an alpha-adrenergic receptor blocker.

This invention is also particularly directed to a method, hereinafter termed "Method AC", of Method A wherein said first compound and said second compound are administered sequentially in either order.

This invention is also particularly directed to a method, hereinafter termed "Method AD", of Method A wherein said first compound and said second compound are administered simultaneously.

This invention is still more particularly directed to a method, hereinafter termed "Method AE", of Method AB wherein said first compound and said second compopund are administered sequentially in either order.

This invention is still more particularly directed to a method, hereinafter termed "Method AF", of Method AB wherein said first compound and said second compound are administered simultaneously.

This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises antianginal treatment.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises antianginal treatment.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises antianginal treatment.

This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises cardiac risk management.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises cardiac risk management.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises cardiac risk management.

This invention is also particularly directed to a method of Method A wherein said therapeutic treatment comprises the treatment of atherosclerosis.

This invention is also particularly directed to a method of Method AE wherein said therapeutic treatment comprises the treatment of atherosclerosis.

This invention is also particularly directed to a method of Method AF wherein said therapeutic treatment comprises the treatment of atherosclerosis.

Amlodipine is a racemic compound due to the symmetry at position 4 of the dihydropyridine ring. The R and S enantiomers may be prepared as described by Arrowsmith et al., J. Med. Chem., 1986, 29, 1696. The calcium channel blocking activity of amlodipine is substantially confined to the S(-) isomer and to the racemic mixture containing the R(+) and S(-) forms. (see International Patent Application Number PCT/EP94/02697). The R(+) isomer has little or no calcium channel blocking activity. However, the R(+) isomer is a potent inhibitor of smooth muscle cell migration. Thus, the R(+) isomer is useful in the treatment or prevention of atherosclerosis. (see International Patent Application Number PCT/EP95/00847). Based on the above, a skilled person could choose the R(+) isomer, the S(-) isomer or the racemic mixture of the R(+) isomer and the S(-) isomer for use in the combination of this invention.

Where used herein, the term "cardiac risk" means the likelihood that a subject will suffer a future adverse cardiac event such as, e.g., myocardial infarction, cardiac arrest, cardiac failure, cardiac ischaemia. Cardiac risk is calculated using the Framingham Risk Equation as set forth above. The term "cardiac risk management" means that the risk of future adverse cardiac events is substantially reduced.

It will be recognized by those skilled in the art that certain of the antihypertensive agents which are used in combination with atorvastatin or a pharmacuetically acceptable salt of atorvastatin contain either an acidic moiety or a basic moiety which may be reacted with either a base to form a cationic salt or an acid to form an acid addtion salt, respectively. All of the pharmaceutically acceptable salts of th antihypertensive agents disclosed herein are within the scope of the combination of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of this invention comprise atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent or a pharmaceutically acceptable salt thereof.

Atorvastatin may readily be prepared as described in U.S. Patent No. 4,681,893, which is incorporated herein by reference. The hemicalcium salt of atorvastatin, which is currently sold as Lipitor®, may readily be prepared as described in U.S. Patent No. 5,273,995, which is incorporated herein by reference.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Besides the hemicalcium salt, other pharmaceutically-acceptable cationic salts of atorvastatin may be readily prepared by reacting the free acid form of atorvastatin with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt f the cation (sodium or potassium thylhexanoate, magnesium oleate), and employing a

solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent. The acid addition salts of atorvastatin may be readily prepared by reacting the free base form of atorvastatin with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition and cationic salts of the antihypertensive agents used in the combination of this invention may be prepared in a manner analogous to that described for the preparation of the pharmaceutically acceptable acid addition and cationic salts of atorvastatin, but substituting the desired antihypertensive compound for atorvastatin.

The antihypertensive agents which may be used in accordance with this invention are members of different classes of antihypertensive agents, including calcium channel blockers (excluding amlodipine and pharmaceutically acceptable acid addition salts thereof), ACE inhibitors, A-II antagonists, diuretics, beta-adrenergic receptor blockers, vasodilators and alpha-adrenergic receptor blockers.

Calcium channel blockers which are within the scope of this invention include, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Patent No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, which may be prepared as disclosed in U.S. Patent No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Patent No. 3,562, fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; mibefradil, which may be prepared as disclosed in U.S. Patent No. 4,808,605; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; semotiadil, which may be prepared as disclosed in U.S. Patent No. 4,786,635; terodiline, which may be prepared as disclosed in U.S. Patent No.

3,371,014; verapamil, which may be prepared as disclosed in U.S. Pat nt No. 3,261,859; aranipine, which may be prepared as disclosed in U.S. Patent No. 4,572,909; barnidipine, which may be prepared as disclosed in U.S. Patent No. 4,220,649; benidipine, which may be prepared as disclosed in European Patent Application Publication No. 106,275; cilnidipine, which may be prepared as disclosed in U.S. Patent No. 4,672,068; efonidipine, which may be prepared as disclosed in U.S. Patent No.4,885,284; elgodipine, which may be prepared as disclosed in U.S. Patent No. 4,952,592; felodipine, which may be prepared as disclosed in U.S. Patent No. 4,264,611; isradipine, which may be prepared as disclosed in U.S. Patent No. 4,466,972; lacidipine, which may be prepared as disclosed in U.S. Patent No. 4,801,599; lercanidipine, which may be prepared as disclosed in U.S. Patent No. 4,705,797; manidipine, which may be prepared as disclosed in U.S. Patent No. 4,892,875; nicardipine, which may be prepared as disclosed in U.S. Patent No. 3,985,758; nifedipine, which may be prepared as disclosed in U.S. Patent No. 3,485,847; nilvadipine, which may be prepared as disclosed in U.S. Patent No. 4,338,322; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; nisoldipine, which may be prepared as disclosed in U.S. Patent No. 4,154,839; nitrendipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; cinnarizine, which may be prepared as disclosed in U.S. Patent No. 2,882,271; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; bencyclane, which may be prepared as disclosed in Hungarian Patent No. 151,865; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; and perhexiline, which may be prepared as disclosed in British Patent No. 1,025,578. The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be prepared as disclosed in U.S. Patent No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Patent No. 4,410,520; captopril, which may be prepared as disclosed in U.S. Patent Nos. 4,046,889 and 4,105,776; ceronapril, which may be prepared as disclosed in U.S. Patent No. 4,452,790; delapril, which

may be prepared as disclosed in U.S. Patent No. 4,385,051; enalapril, which may be prepared as disclosed in U.S. Patent No. 4,374,829; fosinopril, which may be prepared as disclosed in U.S. Patent No. 4,337,201; imadapril, which may be prepared as disclosed in U.S. Patent No. 4,508,727; lisinopril, which may be prepared as disclosed in U.S. Patent No. 4,555,502; moveltopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,729; quinapril, which may be prepared as disclosed in U.S. Patent No. 4,344,949; ramipril, which may be prepared as disclosed in U.S. Patent No. 4,587,258; spirapril, which may be prepared as disclosed in U.S. Patent No. 4,470,972; temocapril, which may be prepared as disclosed in U.S. Patent No. 4,699,905; and trandolapril, which may be prepared as disclosed in U.S. Patent No. 4,933,361. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Patent No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Patent No. 5,185,351; irbesartan, which may be prepared as disclosed in U.S. Patent No. 5,270,317; losartan, which may be prepared as disclosed in U.S. Patent No. 5,138,069; and valsartan, which may be prepared as disclosed in U.S. Patent No. 5,399,578. The disclosures of all such U.S. patents are incorporated herein by reference.

Beta-adrenergic receptor blockers (beta- or β-blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be prepared as disclosed in U.S. Patent No. 3,857,952; alprenolol, which may be prepared as disclosed in Netherlands Patent Application No. 6,605,692; amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,305; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; atenolol, which may be prepared as disclosed in U.S. Patent No. 3,663,607 or 3,836,671; befunolol, which may be prepared as disclosed in U.S. Patent No. 3,853,923; betaxolol, which may be prepared as disclosed in U.S. Patent No. 4,252,984; bevantolol, which may be prepared as disclosed in U.S. Patent No. 3,857,981; bisoprolol, which may be prepared as disclosed in U.S. Patent No. 4,171,370; bopindolol, which may be

prepared as disclosed in U.S. Patent No. 4,340,541; bucumolol, which may be prepared as disclosed in U.S. Patent No. 3,663,570; bufetolol, which may be prepared as disclosed in U.S. Patent No. 3,723,476; bufuralol, which may be prepared as disclosed in U.S. Patent No. 3,929,836; bunitrolol, which may be prepared as disclosed in U.S. Patent Nos. 3,940,489 and 3,961,071; buprandolol, which may be prepared as disclosed in U.S. Patent No. 3,309,406; butiridine hydrochloride, which may be prepared as disclosed in French Patent No. 1,390,056; butofilolol, which may be prepared as disclosed in U.S. Patent No. 4,252,825; carazolol, which may be prepared as disclosed in German Patent No. 2,240,599; carteolol, which may be prepared as disclosed in U.S. Patent No. 3,910,924; carvedilol, which may be prepared as disclosed in U.S. Patent No. 4,503,067; celiprolol, which may be prepared as disclosed in U.S. Patent No. 4,034,009; cetamolol, which may be prepared as disclosed in U.S. Patent No. 4,059,622; cloranolol, which may be prepared as disclosed in German Patent No. 2,213,044; dilevalol, which may be prepared as disclosed in Clifton et al., Journal of Medicinal Chemistry, 1982, 25, 670; epanolol, which may be prepared as disclosed in European Patent Publication Application No. 41,491; indenolol, which may be prepared as disclosed in U.S. Patent No. 4,045,482; labetalol, which may be prepared as disclosed in U.S. Patent No. 4,012,444; levobunolol, which may be prepared as disclosed in U.S. Patent No. 4,463,176; mepindolol, which may be prepared as disclosed in Seeman et al., Helv. Chim. Acta, 1971, 54, 241; metipranolol, which may be prepared as disclosed in Czechoslovakian Patent Application No. 128,471; metoprolol, which may be prepared as disclosed in U.S. Patent No. 3,873,600; moprolol, which may be prepared as disclosed in U.S. Patent No. 3,501,769l; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,935, 267; nadoxolol, which may be prepared as disclosed in U.S. Patent No. 3,819,702; nebivalol, which may be prepared as disclosed in U.S. Patent No. 4,654,362; nipradilol, which may be prepared as disclosed in U.S. Patent No. 4,394,382; oxprenolol, which may be prepared as disclosed in British Patent No. 1,077,603; perbutolol, which may be prepared as disclosed in U.S. Patent No. 3,551,493; pindolol, which may be prepared as disclosed in Swiss Patent Nos. 469,002 and 472,404; practolol, which may be prepared as disclosed in U.S. Patent

No. 3,408,387; pronethalol, which may be prepared as disclosed in British Patent No. 909,357; propranolol, which may be prepared as disclosed in U.S. Patent Nos. 3,337,628 and 3,520,919; sotalol, which may be prepared as disclosed in Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88; sufinalol, which may be prepared as disclosed in German Patent No. 2,728,641; talindol, which may be prepared as disclosed in U.S. Patent Nos. 3,935,259 and 4,038,313; tertatolol, which may be prepared as disclosed in U.S. Patent No. 3,960,891; tilisolol, which may be prepared as disclosed in U.S. Patent No. 4,129,565; timolol, which may be prepared as disclosed in U.S. Patent No. 3,655,663; toliprolol, which may be prepared as disclosed in U.S. Patent No. 3,432,545; and xibenolol, which may be prepared as disclosed in U.S. Patent No. 4,018,824. The disclosures of all such U.S. patents are incorporated herein by reference.

Alpha-adrenergic receptor blockers (alpha- or α-blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; dapiprazole, which may be prepared as disclosed in U.S. Patent No. 4,252,721; doxazosin, which may be prepared as disclosed in U.S. Patent No. 4,188,390; fenspiride, which may be prepared as disclosed in U.S. Patent No. 3,399,192; indoramin, which may be prepared as disclosed in U.S. Patent No. 3,527,761; labetolol, which may be prepared as disclosed above; naftopidil, which may be prepared as disclosed in U.S. Patent No. 3,997,666; nicergoline, which may be prepared as disclosed in U.S. Patent No. 3,228,943; prazosin, which may be prepared as disclosed in U.S. Patent No. 3,511,836; tamsulosin, which may be prepared as disclosed in U.S. Patent No. 4,703,063; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; trimazosin, which may be prepared as disclosed in U.S. Patent No. 3,669,968; and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "vasodilator," where used herein, is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to:

bencyclane, which may be prepared as disclosed above; cinnarizine, which may be prepared as disclosed above; citicoline, which may be isolated from natural sources as disclosed in Kennedy et al., Journal of the American Chemical Society, 1955, 77, 250 or synthesized as disclosed in Kennedy, Journal of Biological Chemistry, 1956, 222, 185; cyclandelate, which may be prepared as disclosed in U.S. Patent No. 3,663,597; ciclonicate, which may be prepared as disclosed in German Patent No. 1,910,481; diisopropylamine dichloroacetate, which may be prepared as disclosed in British Patent No. 862,248; ebumamonine, which may be prepared as disclosed in Hermann et al., Journal of the American Chemical Society, 1979, 101, 1540; fasudil, which may be prepared as disclosed in U.S. Patent No. 4,678,783; fenoxedil, which may be prepared as disclosed in U.S. Patent No. 3,818,021; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; ibudilast, which may be prepared as disclosed in U.S. Patent No. 3,850,941; ifenprodil, which may be prepared as disclosed in U.S. Patent No. 3,509,164; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; nafronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blicke et al., Journal of the American Chemical Society, 1942, 64, 1722; nicergoline, which may be prepared as disclosed above; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; papaverine, which may be prepared as reviewed in Goldberg, Chem. Prod. Chem. News, 1954, 17, 371; pentifylline, which may be prepared as disclosed in German Patent No. 860,217; tinofedrine, which may be prepared as disclosed in U.S. Patent No. 3,563,997; vincamine, which may be prepared as disclosed in U.S. Patent No. 3,770,724; vinpocetine, which may be prepared as disclosed in U.S. Patent No. 4,035,750; and viquidil, which may be prepared as disclosed in U.S. Patent No. 2,500,444. The disclosures of all such U.S. patents are incorporated herein by reference.

Coronary vasodilators within the scope of this invention include, but are not limited to: amotriphene, which may be prepared as disclosed in U.S. Patent No. 3,010,965; bendazol, which may be prepared as disclosed in J. Chem. Soc. 1958, 2426; benfurodil hemisuccinate, which may be prepared as disclosed in U.S. Patent No. 3,355,463; benziodarone, which may be prepared as disclosed in U.S. Patent No. 3,012,042; chloracizine, which may be prepared as disclosed in British Patent No. 740,932; chromonar, which may be prepared as disclosed in U.S. Patent No.

3,282,938; clobenfural, which may be prepared as disclosed in British Patent No. 1,160,925; clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see *Annalen*, **1870**, **155**, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilazep, which may be prepared as disclosed in U.S. Patent No. 3,532,685; dipyridamole, which may be prepared as disclosed in British Patent No. 807,826; droprenilamine, which may be prepared as disclosed in German Patent No. 2,521,113; efloxate, which may be prepared as disclosed in British Patent Nos. 803,372 and 824,547; erythrityl tetranitrate, which may be prepared by nitration of erythritol according to methods well-known to those skilled in the art; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; floredil, which may be prepared as disclosed in German Patent No. 2,020,464; ganglefene, which may be prepared as disclosed in U.S.S.R. Patent No. 115,905; hexestrol, which may be prepared as disclosed in U.S. Patent No. 2,357,985; hexobendine, which may be prepared as disclosed in U.S. Patent No. 3,267,103; itramin tosylate, which may be prepared as disclosed in Swedish Patent No. 168,308; khellin, which may be prepared as disclosed in Baxter et al., Journal of the Chemical Society, 1949, S 30; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; mannitol hexanitrate, which may be prepared by the nitration of mannitol according to methods well-known to those skilled in the art; medibazine, which may be prepared as disclosed in U.S. Patent No. 3,119,826; nitroglycerin; pentaerythritol tetranitrate, which may be prepared by the nitration of pentaerythritol according to methods well-known to those skilled in the art; pentrinitrol, which may be prepared as disclosed in German Patent No. 638,422-3; perhexilline, which may be prepared as disclosed above; pimefylline, which may be prepared as disclosed in U.S. Patent No. 3,350,400; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; propatyl nitrate, which may be prepared as disclosed in French Patent No. 1,103,113; trapidil, which may be prepared as disclosed in East German Patent No. 55,956; tricromyl, which may be prepared as disclosed in U.S. Patent No. 2,769,015; trimetazidine, which may be prepared as disclosed in U.S. Patent No. 3,262,852; trolnitrat phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric

acid according to methods well-known to those skilled in the art; visnadine, which may be prepared as disclosed in U.S. Patent Nos. 2,816,118 and 2,980,699. The disclosures of all such U.S. patents are incorporated herein by reference.

Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminum nicotinate, which may be prepared as disclosed in U.S. Patent No. 2,970,082; bamethan, which may be prepared as disclosed in Corrigan et al., Journal of the American Chemical Society, 1945, 67, 1894; bencyclane, which may be prepared as disclosed above; betahistine, which may be prepared as disclosed in Walter et al.; Journal of the American Chemical Society, 1941, 63, 2771; bradykinin, which may be prepared as disclosed in Hamburg et al., Arch. Biochem. Biophys., 1958, 76, 252; brovincamine, which may be prepared as disclosed in U.S. Patent No. 4,146,643; bufeniode, which may be prepared as disclosed in U.S. Patent No. 3,542,870; buflomedil, which may be prepared as disclosed in U.S. Patent No. 3,895,030; butalamine, which may be prepared as disclosed in U.S. Patent No. 3,338,899; cetiedil, which may be prepared as disclosed in French Patent Nos. 1,460,571; ciclonicate, which may be prepared as disclosed in German Patent No. 1,910,481; cinepazide, which may be prepared as disclosed in Belgian Patent No. 730,345; cinnarizine, which may be prepared as disclosed above; cyclandelate, which may be prepared as disclosed above; diisopropylamine dichloroacetate, which may be prepared as disclosed above; eledoisin, which may be prepared as disclosed in British Patent No. 984,810; fenoxedil, which may be prepared as disclosed above; flunarizine, which may be prepared as disclosed above; hepronicate, which may be prepared as disclosed in U.S. Patent No. 3,384,642; ifenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,692,464; inositol niacinate, which may be prepared as disclosed in Badgett et al., Journal of the American Chemical Society, 1947, 69, 2907; isoxsuprine, which may be prepared as disclosed in U.S. Patent No. 3,056,836; kallidin, which may be prepared as disclosed in *Biochem. Biophys. Res. Commun.*, 1961, 6, 210; kallikrein, which may be prepared as disclosed in German Patent No. 1,102,973; moxisylyte, which may be prepared as disclosed in German Patent No. 905,738; nafronyl, which may be prepared as disclosed above; nicametate, which may be prepared as disclosed above; nicergoline, which may be prepared as disclosed above; nicofuranose, which may be prepared as disclosed in Swiss Patent

No. 366,523; nylidrin, which may be prepared as disclosed in U.S. Patent Nos. 2,661,372 and 2,661,373; pentifylline, which may be prepared as disclosed above; pentoxifylline, which may be prepared as disclosed in U.S. Patent No. 3,422,107; piribedil, which may be prepared as disclosed in U.S. Patent No. 3,299,067; prostaglandin E_1, which may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budaveri, Ed., New Jersey, 1996, p. 1353; suloctidil, which may be prepared as disclosed in German Patent No. 2,334,404; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; and xanthinol niacinate, which may be prepared as disclosed in German Patent No. 1,102,750 or Korbonits et al., Acta. Pharm. Hung., 1968, 38, 98. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "diuretic," within the scope of this invention, is meant to include diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine, which may be prepared as disclosed in Austrian Patent No. 168,063; amiloride, which may be prepared as disclosed in Belgian Patent No. 639,386; arbutin, which may be prepared as disclosed in Tschitschibabin, Annalen, 1930, 479, 303; chlorazanil, which may be prepared as disclosed in Austrian Patent No. 168,063; ethacrynic acid, which may be prepared as disclosed in U.S. Patent No. 3,255,241; etozolin, which may be prepared as disclosed in U.S. Patent No. 3,072,653; hydracarbazine, which may be prepared as disclosed in British Patent No. 856,409; isosorbide, which may be prepared as disclosed in U.S. Patent No. 3,160,641; mannitol; metochalcone, which may be prepared as disclosed in Freudenberg et al., Ber., 1957, 90, 957; muzolimine, which may be prepared as disclosed in U.S. Patent No. 4,018,890; perhexiline, which may be prepared as disclosed above; ticrynafen, which may be prepared as disclosed in U.S. Patent No. 3,758,506; triamterene which may be prepared as disclosed in U.S. Patent No. 3,081,230; and urea. The disclosures of all such U.S. patents are incorporated herein by reference.

Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide, which may be prepared as disclosed in British Patent No. 902,658; bendroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,265,573; benzthiazide, McManus et al., 136th Am. Soc. Meeting

(Atlantic City, September 1959), Abstract of papers, pp 13-O; benzylhydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,108,097; buthiazide, which may be prepared as disclosed in British Patent Nos. 861,367 and 885,078; chlorothiazide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194 and 2,937,169; chlorthalidone, which may be prepared as disclosed in U.S. Patent No. 3,055,904; cyclopenthiazide, which may be prepared as disclosed in Belgian Patent No. 587,225; cyclothiazide, which may be prepared as disclosed in Whitehead et al., Journal of Organic Chemistry, 1961, 26, 2814; epithiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; ethiazide, which may be prepared as disclosed in British Patent No. 861,367; fenquizone, which may be prepared as disclosed in U.S. Patent No. 3,870,720; indapamide, which may be prepared as disclosed in U.S. Patent No. 3,565,911; hydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,164,588; hydroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,254,076; methyclothiazide, which may be prepared as disclosed in Close et al., Journal of the American Chemical Society, 1960, 82, 1132; meticrane, which may be prepared as disclosed in French Patent Nos. M2790 and 1,365,504; metolazone, which may be prepared as disclosed in U.S. Patent No. 3,360,518; paraflutizide, which may be prepared as disclosed in Belgian Patent No. 620,829; polythiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; quinethazone, which may be prepared as disclosed in U.S. Patent No. 2,976,289; teclothiazide, which may be prepared as disclosed in Close et al., Journal of the American Chemical Society, 1960, 82, 1132; and trichlormethiazide, which may be prepared as disicosed in deStevens et al., Experientia, 1960, 16, 113. The disclosures of all such U.S. patents are incorporated herein by reference.

Diuretic sulfonamide derivatives within the scope of this invention include, but are not limited to: acetazolamide, which may be prepared as disclosed in U.S. Patent No. 2,980,679; ambuside, which may be prepared as disclosed in U.S. Patent No. 3,188,329; azosemide, which may be prepared as disclosed in U.S. Patent No. 3,665,002; bumetanide, which may be prepared as disclosed in U.S. Patent No. 3,634,583; butazolamide, which may be prepared as disclosed in British Patent No. 769,757; chloraminophenamide, which may be prepared as disclosed in U.S. Pat nt Nos. 2,809,194, 2,965,655 and 2,965,656; clofenamide, which may be prepared as

disclosed in Olivier, Rec. Trav. Chim., 1918, 37, 307; clopamide, which may be prepared as disclosed in U.S. Patent No. 3,459,756; clorexolone, which may be prepared as disclosed in U.S. Patent No. 3,183,243; disulfamide, which may be prepared as disclosed in British Patent No. 851,287; ethoxolamide, which may be prepared as disclosed in British Patent No. 795,174; furosemide, which may be prepared as disclosed in U.S. Patent No. 3,058,882; mefruside, which may be prepared as disclosed in U.S. Patent No. 3,356,692; methazolamide, which may be prepared as disclosed in U.S. Patent No. 2,783,241; piretanide, which may be prepared as disclosed in U.S. Patent No. 4,010,273; torasemide, which may be prepared as disclosed in U.S. Patent No. 4,018,929; tripamide, which may be prepared as disclosed in Japanese Patent No. 73 05,585; and xipamide, which may be prepared as disclosed in U.S. Patent No. 3,567,777. The disclosures of all such U.S. patents are incorporated herein by reference.

In addition, atorvastatin and pharmaceutically acceptable salts thereof may occur as hydrates or solvates. Further, the antihypertensive agents which may be used in accordance with this invention and the pharmaceutically acceptable salts thereof may occur as hydrates or solvates. Said hydrates and solvates are also within the scope of the invention.

The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents in the treatment of atherosclerosis, angina pectoris, and a condition characterized by the presence of both hypertension and hyperlipidemia in mammals, particularly humans. Further, since these diseases and conditions are closely related to the development of cardiac disease and adverse cardiac conditions, these combinations and methods, by virtue of their action as antiatherosclerotics, antianginals, antihypertensives and antihyperlipidemics, are useful in the management of cardiac risk.

The utility of the compounds of the present invention as medical agents in the treatment of atherosclerosis in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Atorvastatin and an Antihypertensive Agent, Alone and in Combination, on the Treatment

of Atherosclerosis

This study is a prospective randomized evaluation of the effect of a combination of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent on the progression/regression of coronary and carotid artery disease. The study is used to show that a combination of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent is effective in slowing or arresting the progression or causing regression of existing coronary artery disease (CAD) as evidenced by changes in coronary angiography or carotid ultrasound, in subjects with established disease.

This study is an angiographic documentation of coronary artery disease carried out as a double-blind, placebo-controlled trial of a minimum of about 500 subjects and preferably of about 780 to about 1200 subjects. It is especially preferred to study about 1200 subjects in this study. Subjects are admitted into the study after satisfying certain entry criteria set forth below.

Entry criteria: Subjects accepted for entry into this trial must satisfy certain criteria. Thus the subject must be an adult, either male or female, aged 18-80 years of age in whom coronary angiography is clinically indicated. Subjects will have angiographic presence of a significant focal lesion such as 30% to 50% on subsequent evaluation by quantitative coronary angiography (QCA) in a minimum of one segment (non-PTCA, non-bypassed or non-MI vessel) that is judged not likely to require intervention over the next 3 years. It is required that the segments undergoing analysis have not been interfered with. Since percutaneous transluminal cardiac angioplasty (PTCA) interferes with segments by the insertion of a balloon catheter, non-PTCA segments are required for analysis. It is also required that the segments to be analyzed have not suffered a thrombotic event, such as a myocardial infarct (MI). Thus the requirement for non-MI vessels. Segments that will be analyzed include: left main, proximal, mid and distal left anterior descending, first and second diagonal branch, proximal and distal left circumflex, first or largest space obtuse marginal, proximal, mid and distal right coronary artery. Subjects will have an ejection fraction of greater than 40% determined by catheterization or radionuclide ventriculography or ECHO cardiogram at the time of the qualifying angiogram or within the previous three months of the acceptance of the qualifying angiogram

provided no intervening event such as a thrombotic event or procedure such as PTCA has occurred.

Generally, due to the number of patients and the physical limitations of any one facility, the study is carried out at multiple sites. At entry into the study, subjects undergo quantitative coronary angiography as well as B-mode carotid artery ultrasonography and assessment of carotid arterial compliance at designated testing centers. This establishes baselines for each subject. Once admitted into the test, subjects are randomized to receive an antihypertensive agent or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive agent or salt thereof chosen) and placebo or atorvastatin calcium (80 mgs) and placebo or an antihypertensive agent or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive agent or salt thereof chosen) and atorvastatin calcium (80 mgs). It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statinand amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The amount of the antihypertensive agent may be varied as required. The amount of the statin will be titrated down from 80 mg if it is determined by the physician to be in the best interests of the subject. The subjects are monitored for a one to three year period, generally three years being preferred. B-mode carotid ultrasound assessment of carotid artery atherosclerosis and compliance are performed at regular intervals throughout the study.

Generally, six month intervals are suitable. Typically this assessment is performed using B-mode ultrasound equipment. However, a person skilled in the art may use other methods of performing this assessment. Coronary angiography is performed at the conclusion of the one to three year treatment period. The baseline and post-treatment angiograms and the intervening carotid artery B-mode ultrasonograms are evaluated for new lesions or progression of existing atherosclerotic lesions. Arterial compliance measurements are assessed for changes from baselin and over the 6-month evaluation periods.

The primary objectiv of this study is to show that the combination of an antihypertensiv agent and atorvastatin reduces the progression of atherosclerotic

lesions as measured by quantitative coronary angiography (QCA) in subjects with clinical coronary artery disease. QCA measures the opening in the lumen of the arteries measured.

The primary endpoint of the study is the change in the average mean segment diameter of the coronary artery tree. Thus, the diameter of an arterial segment is measured at various portions along the length of that segment. The average diameter of that segment is then determined. After the average segment diameter of many segments has been determined, the average of all segment averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking atorvastatin or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will decline more slowly, will be halted completely, or there will be an increase in the mean segment diameter. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, repsectively.

The secondary objective of this study is that the combination of an antihypertensive agent and atorvastatin or a pharmaceutically acceptable salt thereof reduces the rate of progression of atherosclerosis in the carotid arteries as measured by the slope of the maximum intimal-medial thickness measurements averaged over 12 separate wall segments (Mean Max) as a function of time, more than does amlodipine or a pharmaceutically acceptable acid addition salt thereof or atorvastatin or a pharmaceutically acceptable salt thereof alone. The intimal-medial thickness of subjects taking atorvastatin or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will increase more slowly, will cease to increase or will decrease. These results represent slowed prorgression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively. Further, these results may be used to facilitate dosage determinations.

The utility of the compounds of the present invention as medical agents in the treatment of angina pectoris in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Atorvastatin and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Angina

This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in the treatment of symptomatic angina.

Entry criteria: Subjects are males or females between 18 and 80 years of age with a history of typical chest pain associated with one of the following objective evidences of cardiac ischemia: (1) stress test segment elevation of about one millimeter or more from the ECG; (2) positive treadmill stress test; (3) new wall motion abnormality on ultrasound; or (4) coronary angiogram with a significant qualifying stenosis. Generally a stenosis of about 30-50% is considered to be significant.

Each subject is evaluated for about ten to thirty-two weeks. At least ten weeks are generally required to complete the study. Sufficient subjects are used in this screen to ensure that about 200 to 800 subjects and preferably about 400 subject are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth below, during a four week run in phase. After the screening criteria are met, subjects are washed out from their current anti-anginal medication and stabilized on a long acting nitrate such as nitroglycerine, isosorbide-5-mononitrate or isosorbide dinitrate. The term "washed out", when used in connection with this screen, means the withdrawal of current anti-anginal medication so that substantially all of said medication is eliminated from the body of the subject. A period of eight weeks is preferably allowed for both the wash out period and for the establishment of the subject on stable doses of said nitrate. Subjects having one or two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the wash out phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. In the randomization phase, the subjects are randomly placed into one of the four arms of the study set forth below. After completing the wash out phase, subjects in compliance with the entry criteria undergo twenty four hour ambulatory electrocardigram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial

perfusion using PET (photon emission tomography) scanning to establish a baseline for each subject. When conducting a stress test, the speed of the treadmill and the gradient of the treadmill can be controlled by a technician. The speed of the treadmill and the angle of the gradient are generally increased during the test. The time intervals between each speed and gradient increase is generally determined using a modified Bruce Protocol.

After the baseline investigations have been completed, subjects are initiated on one of the following four arms of the study: (1) placebo; (2) atorvastatin (about 10 mg to about 80 mg); (3) an antihypertensive agent (dose is dependent upon the particular antihypertensive agent chosen); or (4) a combination of the above doses of atorvastatin and antihypertensive agent together. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statinand amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The subjects are then monitored for two to twenty four weeks.

After the monitoring period has ended, subjects will undergo the following investigations: (1) twenty four hour ambulatory ECG, such as Holter monitoring; (2) exercise stress testing (e.g. treadmill using said modified Bruce Protocol); and (3) evaluation of myocardial perfusion using PET scanning. Patients keep a diary of painful ischemic events and nitroglycerine consumption. It is generally desirable to have an accurate record of the number of anginal attacks suffered by the patient during the duration of the test. Since a patient generally takes nitroglycerin to ease the pain of an anginal attack, the number of times that the patient administers nitroglycerine provides a reasonably accurate record of the number of anginal attacks.

To demonstrate the effectiveness and dosage of the drug combination of this invention, the person conducting the test will evaluate the subject using the tests described. Successful treatment will yield fewer instances of ischemic events as detected by ECG, will allow the subject to exercise longer or at a higher intensity level on the treadmill, or to exercise without pain on the treadmill, or will yield better perfusion or fewer perfusion defects on ultrasound.

The utility of the compounds of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effect of Atorvastatin and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Subjects Having Both Hypertension and Hyperlipidemia

This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are used in this screen to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects are male or female adults between 18 and 80 years of age having both hyperlipidemia and hypertension. The presence of hyperlipidemia is evidenced by evaluation of the low density lipoprotein (LDL) level of the subject relative to certain positive risk factors. If the subject has no coronary heart disease (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 190. If the subject has no CHD and has two or more positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 160. If the subject has CHD, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 130.

Positive risk factors include (1) male over 45, (2) female over 55 wherein said female is not undergoing hormone replacement therapy (HRT), (3) family history of premature cardiovascular disease, (4) the subject is a current smoker, (5) the subject has diabetes, (6) an HDL of less than 45, and (7) the subject has hypertension. An HDL of greater than 60 is considered a negative risk factor and will offset one of the above mentioned positive risk factors.

The presence of hypertension is evidenced by a sitting diastolic blood pressure (BP) of greater than 90 or sitting systolic BP of greater than 140. All blood pressures are generally determined as the average of three measurements taken five minutes apart.

Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, subjects are washed out from their current antihypertensive and lipid lowering medication and are placed on the NCEP ATP II Step 1 diet. The NCEP ATP II (adult treatment panel, 2nd revision) Step 1 diet sets forth the amount of saturated and unsaturated fat which can be consumed as a proportion of the total caloric intake. The term "washed out" where used in connection with this screen, means the withdrawal of current antihypertensive and lipid lowering medication so that substantially all of said medication is eliminated from the body of the subject. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid screen determines baseline lipid levels in the fasting state of a subject. Generally, the subject abstains from food for twelve hours, at which time lipid levels are measured.

After the baseline investigations are performed subjects are started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of atorvastatin, generally about 10 to 80mg; or (3) a combination of the above doses of atorvastatin and an antihypertensive agent together. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statinand amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Subjects remain on these doses for a minimum of six weeks, and generally for no more than eight weeks. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at the conclusion of the study is compared with the blood pressure of the subject upon ntry. The lipid screen

measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, VLDL (very low density lipoprotein) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination.

The utility of the compounds of the present invention as medical agents in the management of cardiac risk in mammals (e.g., humans) at risk for an adverse cardiac event is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

Effects of Atorvastatin and an Antihypertensive Agent, Alone and in Combination, on Subjects at Risk of Future Cardiovascular Events

This study is a double blind, parallel arm, randomized study to show the effectiveness of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in reducing the overall calculated risk of future events in subjects who are at risk for having future cardiovascular events. This risk is calculated by using the Framingham Risk Equation. A subject is considered to be at risk of having a future cardiovascular event if that subject is more than one standard deviation above the mean as calculated by the Framingham Risk Equation. The study is used to evaluate the efficacy of a fixed combination of atorvastatin or a pharmaceutically acceptable salt thereof and an antihypertensive agent in controlling cardiovascular risk by controlling both hypertension and hyperlipidemia in patients who have both mild to moderate hypertension and hyperlipidemia.

Each subjectis evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are recruited to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects included in the study are male or female adult subjects between 18 and 80 years of age with a baseline five year risk which risk is above the median for said subject's age and sex, as defined by the Framingham Heart Study, which is an ongoing prospective study of adult men and women showing that certain risk factors can be used to predict the development of coronary heart disease. The age, sex, systolic and diastolic blood pressure, smoking habit, presence or absence of carbohydrate intol rance, presence or absence of left ventricular hypertrophy, serum cholesterol and high density lipoprotein (HDL) of more than on standard

deviation above the norm for the Framingham Population are all evaluated in determining whether a patient is at risk for adverse cardiac event. The values for the risk factors are inserted into the Framingham Risk equation and calculated to determine whether a subject is at risk for a future cardiovascular event.

Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, patients are washed out from their current antihypertensive and lipid lowering medication and any other medication which will impact the results of the screen. The patients are then placed on the NCEP ATP II Step 1 diet, as described above. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP ATP II Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure; (2) fasting; (3) lipid screen; (4) glucose tolerance test; (5) ECG; and (6) cardiac ultrasound. These tests are carried out using standard procedures well known to persons skilled in the art. The ECG and the cardiac ultrasound are generally used to measure the presence or absence of left ventricular hypertrophy.

After the baseline investigations are performed patients will be started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of atorvastatin (about 10 to 80mg); or (3) the combination of the above doses of atorvastatin and an antihypertensive agent. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statinand amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Patients are kept on these doses and are asked to return in six to eight weeks so that the baseline evaluations can be repeated. At this time the new values are entered into the Framingham Risk equation to determine whether the subject has a lower, greater or no change in the risk of future cardiovascular event.

The above assays demonstrating the effectiveness of amodipine or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of

cardiac risk, also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The following dosage amounts and other dosage amounts set forth elsewhere in this specification and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject and the presence of diseases, e.g., diabetes, in the subject. All doses set forth herein, and in the appendant claims, are daily doses.

In general, in accordance with this invention, the below-listed antihypertensive agent is administered in the following dosage amounts:

diltiazem, generally about 120 mg to about 480 mg;
verapamil, generally about 20 mg to about 48 mg;
felodipine, generally about 2.5 mg to about 40 mg;
isradipine, generally about 2.5 mg to about 40 mg;
lacidipine, generally about 1 mg to about 6 mg;
nicardipine, generally about 32 mg to about 120 mg;
nifedipine, generally about 10 mg to about 120 mg;
nimodipine, generally about 120 mg to about 480 mg;
nisoldipine, generally about 5 mg to about 80 mg;
nitrendipine, generally about 5 mg to about 20 mg;
benazepril, generally about 10 mg to about 80 mg;
captopril, generally about 50 mg to about 150 mg;
enalapril, generally about 5 mg to about 40 mg;
fosinopril, generally about 10 mg to about 80 mg;
lisinopril, generally about 10 mg to about 80 mg;

addition salt thereof and atorvastatin or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet. however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

PRODUCT CLAIMS

1. A pharmaceutical composition comprising:

a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof;

b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof; and

c. a pharmaceutically acceptable carrier or diluent;

provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

2. A pharmaceutical composition of claim 1 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

3. A pharmaceutical composition of claim 2 comprising the hemicalcium salt of atorvastatin.

4. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine or a pharmaceutically acceptable salt of said calcium channel blocker.

5. A pharmaceutical composition of claim 4 wherein said calcium channel blocker is felodipine, nifedipine or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan or a pharmaceutically acceptable salt of said A-II antagonist.

7. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride, bendroflumethiazide or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, capopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, trandolapril or a pharmaceutically acceptalbe salt thereof.

10. A pharmaceutical composition of claim 3 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha-adrenergic receptor blocker being doxazosin, prazosin, trimazosin or a pharmaceutically acceptable salt thereof.

11. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antiphypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition of claim 11 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

13. A pharmaceutical composition of claim 12 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

14. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimoldipine, nisoldipine, nitrendipine or felodipine.

15. A pharmaceutical composition of claim 14 wherein said calcium channel blocker is felodipine or nifedipine.

16. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan, irbesartan or valsartan.

17. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

18. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

19. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or trandolapril.

20. A pharmaceutical composition of claim 13 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha blocker being doxazosin, prazosin or trimazosin.

21. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the sum of the therapeutic effect achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

22. A pharmaceutical composition of claim 21 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

23. A pharmaceutical composition of claim 22 comprising the hemicalcium salt of atorvastatin.

24. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a calcium channel blocker, said calcium channel blocker being verapamil, diltiazem, mibefradil, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine or felodipine.

25. A pharmaceutical composition of claim 24 wherein said calcium channel blocker is felodipine or nifedipine.

26. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is an A-II antagonist, said A-II antagonist being losartan irbesartan or valsartan.

27. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a diuretic, said diuretic being amiloride or bendroflumethiazide.

28. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is a beta-adrenergic receptor blocker, said beta-adrenergic receptor blocker being carvedilol.

29. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is an ACE inhibitor, said ACE inhibitor being benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or trandolapril.

30. A pharmaceutical composition of claim 23 wherein said antihypertensive agent is an alpha-adrenergic receptor blocker, said alpha blocker being doxazosin, prazosin or trimazosin.

31. A pharmaceutical composition of claim 11 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

32. A pharmaceutical composition of claim 13 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

33. A pharmaceutical composition of claim 21 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

34. A pharmaceutical composition of claim 23 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

35. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

36. A pharmaceutical composition of claim 35 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

37. A pharmaceutical composition of claim 36 wherein said second pharmaceutical composition comprises the hemicalcium salt of atorvastatin.

38. A pharmaceutical composition of claim 35 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

39. A pharmaceutical composition of claim 37 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

40. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof, which effect is greater than the therapeutic effect achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of atorvastatin or

a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

41. A pharmaceutical composition of claim 40 wherein said antihypertensive agent is a calcium channel blocker, an ACE inhibitor, an A-II antagonist, a diuretic, a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker.

42. A pharmaceutical composition of claim 41 comprising the hemicalcium salt of atorvastatin.

43. A pharmaceutical composition of claim 40 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

44. A pharmaceutical composition of claim 42 wherein said therapeutic effect is antianginal; antiatherosclerotic; antihypertensive and hypolipidemic; or is effective for cardiac risk management.

45. A kit for achieving a therapeutic effect in a mammal comprising:

a. an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of an antihypertensive agent or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. container means for containing said first and second dosage forms, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

46. A kit of claim 45 comprising the hemicalcium salt of atorvastatin.

47. A method for treating a mammal in need of therapeutic treatment comprising administering to said mammal

(a) an amount of a first compound, said first compound being atorvastatin or a pharmaceutically acceptable salt thereof; and

(b) an amount of a second compound, said second compound being an antihypertensive agent or a pharmaceutically acceptable salt thereof;

wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier or diluent, provided that said antihypertensive agent is not amlodipine or a pharmaceutically acceptable acid addition salt thereof.

48. A method of claim 47 comprising the hemicalcium salt of atorvastatin.

49. A method of claim 47 wherein said therapeutic treatment comprises antihypertensive and antihyperlipidemic treatment.

50. A method of claim 47 wherein said therapeutic treatment comprises antianginal treatment.

51. A method of claim 47 wherein said therapeutic treatment comprises cardiac risk management.

52. A method of claim 47 wherein said therapeutic treatment comprises the treatment of atherosclerosis.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IB 98/01230

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 //(A61K31/40,31:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 543 542 A (LAWRENCE R MICHAEL ET AL) 6 August 1996	1-44
A	*cf. col. 31, lines 25-35 and col. 32, lines 17-23*	45-52
A	EP 0 753 298 A (SANKYO CO) 15 January 1997 *cf. abstract, page 6, lines 4-6 and claim 1*	1-52
A	WO 97 16184 A (WARNER LAMBERT CO ;BOCAN THOMAS M A (US)) 9 May 1997 *cf. abstract*	1-52

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 1998	04/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stoltner, A

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INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/IB 98/01230

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GANOTAKIS E.S., ET AL.: "Cardiovascular risk factor management-new drugs will provide a bright future." JOURNAL OF DRUG DEVELOPMENT AND CLINICAL PRACTICE, vol. 8, no. 2, September 1996, pages 57-60, XP002084032 *cf. page 59, right col., 2nd para.*	1-52

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INTERNATIONAL SEARCH REPORT

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